

# Symptomatic diagnosis of prostate cancer in primary care: a structured review

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## SUMMARY

**Background:** Prostate cancer has the second highest cancer incidence and mortality in European men. Most prostate cancers are diagnosed after lower urinary tract symptoms (LUTS) are presented to primary care, but such symptoms more often have a benign cause. A general practitioner (GP) has to try and identify which of these patients have prostate cancer.

**Aims:** To review the presenting features of symptomatic prostate cancer.

**Design of study:** Structured review.

**Method:** We searched Medline from 1980 to 2003 for symptoms, signs, and investigations reported in prostate cancer. This list was then expanded by secondary searches of reference lists. We excluded studies on post-diagnostic topics, such as staging, treatment, and prognosis; studies on non-Western patients; and studies on investigations that are not available in primary care. A second cycle of exclusions removed studies whose results would not guide a GP in deciding whether a patient has prostate cancer.

**Results:** No studies from primary care compared prostate cancer patients directly with controls. Two secondary care studies had enough information to allow a comparison of symptoms in cases compared with controls. In these studies, symptoms were generally more prevalent in cases, but the differences were small. Screening and secondary care studies suggest that early prostate cancer is symptomless, and that locally advanced cancer has LUTS that are similar to those for benign prostatic hypertrophy.

**Conclusion:** There is a very weak evidence base for the primary care diagnosis of prostate cancer in men with lower urinary tract symptoms.

**Keywords:** diagnosis; prostate cancer; signs and symptoms; urinary tract.

## Introduction

APPROXIMATELY one in 14 men are diagnosed with prostate cancer during their lifetime. However, post-mortem studies show that by 50 years of age half of all men have some of the histological changes associated with prostate cancer, and this increases to three-quarters of men by the age of 85 years.<sup>1</sup> The contrast between these figures explains many of the reported epidemiological changes over the past three decades.

The incidence of diagnosed prostate cancer rose steeply from 1970 to 1995,<sup>2-4</sup> but has decreased slightly since then. The first phase of the increase was mainly due to the discovery of clinically unsuspected cancers at routine prostatectomy,<sup>5,6</sup> with some contribution from postmortem findings in men who had died from other causes.<sup>7,1</sup> A second increase occurred in the 1990s, as prostate-specific antigen (PSA) testing was introduced as a method of screening.<sup>8-10</sup> In the United States (US), where PSA screening has gained wide acceptance, the incidence of prostate cancer is now higher than for male lung cancer.<sup>11</sup> In Europe, prostate cancer incidence remains below that for lung cancer. Approximately 1% of 80-year-old men are diagnosed with prostate cancer each year.<sup>12</sup> A general practice in the United Kingdom (UK) with a list size of 7000 patients would expect have two new diagnoses of prostate cancer every year.<sup>13</sup> Prostate cancer has a relatively high 5-year survival rate of approximately 50%,<sup>4</sup> but despite this, it still ranks second in male cancer mortality in both Europe and the US.<sup>14-16</sup>

Most cancers arise in the periphery of the prostate gland, and cause symptoms only when they have grown to compress the urethra, or invade the sphincter or neurovascular bundle.<sup>5,17</sup> The stage of the cancer is helpful in understanding what symptoms (if any) it produces. Four staging systems have been described, and the tumour, node, metastasis (TNM) system is the most widely used.<sup>18</sup> In the TNM system, T1 tumours are by definition clinically silent; T2 are palpable rectally, T2a tumours are confined to one lobe and are less than 1.5 cm in size, and T2b are diffuse, larger, or present in both lobes; T3 tumours have invaded local structures, such as the bladder, seminal vesicles or the prostatic capsule; and T4 tumours have invaded more widely.

## Purpose of the review

This review addresses the symptomatic presentation of primary prostate cancer. Prostate cancer diagnosis takes one of the following three main routes: asymptomatic diagnosis following a screening test, symptomatic diagnosis with lower urinary tract symptoms (LUTS), or presentation with metastases. The term LUTS has replaced the word 'prostatism', as

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**HOW THIS FITS IN***What do we know?*

Most prostate cancers in Europe are diagnosed after initial presentation to primary care with symptoms. However, similar symptoms can occur with benign conditions.

*What does this paper add?*

No symptom is helpful in distinguishing prostate cancer from benign prostatic hypertrophy. Rectal examination and prostate-specific antigen testing may do so, but the use of the latter remains controversial.



not all urinary symptoms in older men are caused by enlargement of the prostate.<sup>19</sup> In Europe, the majority of prostate cancers are diagnosed after presentation with symptoms.<sup>20</sup> LUTS are very common, with or without an accompanying cancer, and the differentiation between benign and malignant conditions is important as there are effective treatments for most benign causes of LUTS.<sup>21</sup> Also, although it has not been demonstrated that patients benefit from accelerated diagnosis of early prostate cancer, there is broad agreement on the benefits of the treatment of locally advanced tumours.

Asymptomatic diagnosis and presentation with metastases are not reviewed, but for different reasons. Screening, and in particular prostate-specific antigen (PSA) testing, has been well reviewed, but still generates widely differing opinions.<sup>22-25</sup> Consensus is unlikely until the results of trials involving screening, notably the prostate testing for cancer and treatment ( ProtecT ) trial, are published.<sup>26</sup> Conversely, the research literature on primary care diagnosis of metastatic prostate cancer is very sparse, and is mostly in the form of case reports of atypical presentations of secondary cancer.<sup>27</sup> It is likely that recognition of metastatic cancer will remain part of clinical acumen for the foreseeable future, rather than being illuminated by research publications.<sup>28,29</sup>

**Search strategy**

Systematic searches for symptoms are difficult, particularly for primary care, although strategies for searching on diagnostic tests have been published.<sup>30-32</sup> We searched Medline from 1980 to 2003 for symptoms, signs, and investigations reported in association with prostate cancer. Search terms were: prostate cancer, primary health care, predictive values, and the individual symptoms. The list of studies retrieved was then expanded by secondary searches of reference lists. From these searches, a master list of over 2000 possible studies was compiled. A first cycle of exclusions was applied to remove studies on post-diagnostic topics, such as staging, treatment, or prognosis; on non-Western patients; and on investigations that are not available in primary care, such as computed tomography (CT) scanning. Trials of treatment including an untreated arm were retained.

Relevant information could be contained in several diverse types of study, such as cohort studies or randomised controlled trials. Formal filtering procedures using MeSH terms were unhelpful, as all strategies led to the deletion of pertinent

studies. Therefore, a second cycle of exclusions was more subjective. One researcher applied the question 'Could the result of this study inform a general practitioner in deciding whether a patient has prostate cancer?' to the abstract of each study. Although subjective, this stage was deemed necessary to retain the focus of the review question. After this exclusion 219 studies remained. No attempt was made to combine data statistically, as the study populations were very diverse.

**The clinical problem**

The majority of cancers of the prostate in the UK are diagnosed following presentation with LUTS. Although the general practitioner (GP), and the patient, may consider prostate cancer as a possible cause of LUTS, the probability is that a man with urinary frequency, hesitancy, and a poor urinary stream has benign prostatic hypertrophy (BPH) or detrusor instability.<sup>21</sup> We attempted to identify features that separate prostate cancer from other conditions, particularly BPH.<sup>33</sup>

*The relationship between prostate cancer and BPH*

In practice, prostate cancer frequently coexists with BPH, as both are common. Cancer may be discovered as an unexpected finding after prostatectomy for BPH, although the proportion of cancers uncovered in this way has decreased markedly with the near universal use of PSA testing in urology clinics.<sup>34,35</sup> Studies of the association between BPH and cancer suggest that there is little or no true association between the two.<sup>17,36-40</sup> However, even though having BPH does not make prostate cancer more likely, it does increase the chance of uncovering an incidental cancer. Most men with LUTS and an enlarged prostate will have their PSA tested (either by their GP or after specialist referral) and so some prostate cancers will be found even though the symptoms are not caused by the cancer. Some of the apparent link between LUTS and cancer is, therefore, an artefact. This conflating of the two conditions means that the symptoms of BPH and prostate cancer are often impossible to separate in research reports.

**Individual LUTS**

Studies have tried to determine whether there are any symptoms that predict prostate cancer as distinct from BPH.<sup>41,42</sup> One problem encountered was that hospital series collect together all cases of prostate cancers, however the diagnosis was made. Given that the percentage of cancers found after a prostatectomy for apparent BPH has only fallen recently, and has been as high as 50%, these case series inevitably contain many cases in which patients have simply described their BPH symptoms.<sup>43</sup>

Taking one symptom, a poor urinary stream, as an example, the number of men reporting this symptom in surveys of the general population varies from 12 to 53%.<sup>44-50</sup> Similar figures are found for other symptoms, such as urgency.<sup>44-54</sup> This wide range arises in part from the different ages of the populations studied and the exact question asked. In only two studies were the same questions asked of patients with

Table 1. Symptoms reported by untreated cancer patients and men without cancer.

Symptom	Adolfsson, 1998 <sup>52</sup> (139 patients with untreated cancer, 314 controls without cancer)				Fransson, 2001 <sup>54</sup> (49 patients with untreated cancer, 68 controls without cancer)		
	Number of cancer patients with symptom (%)	Number of controls with symptom (%)	Likelihood ratio (95% CI) <sup>a</sup>	P-value <sup>a</sup>	Mean score for cancer patients <sup>a</sup>	Mean score for controls	P-value <sup>a</sup>
Hesitancy	47/125 (38)	65/295 (22)	1.7 (1.3 to 2.3)	0.001	1.2	0.7	0.06
Leakage	37/122 (30)	42/291 (14)	2.1 (1.5 to 3.0)	<0.001	0.6	0.2	0.04
Urgency	42/121 (35)	39/283 (14)	2.5 (1.8, 3.6)	<0.001	1.3	0.4	0.002
Dysuria	14/122 (12)	8/285 (3)	4.1 (1.9 to 8.7)	0.002	0.2	0.2	1
Weak stream	61/124 (49)	124/286 (43)	1.1 (0.9 to 1.5)	0.25	-	-	-
Frequency	-	-	-	-	7.6	6.3	<0.001

<sup>a</sup>P-values, likelihood ratios and CI recalculated from the data given in the papers for these two groups of interest:  $\chi^2$  for Adolfsson, *t*-test for Fransson.

untreated cancer and controls without cancer.<sup>52,54</sup> The focus of both these studies was to compare symptoms across various treatments, but both included a delayed-treatment group and an age-matched control group without prostate cancer. The studies were similar — they were both Swedish, and used self-administered postal questionnaires. The reply rate for Adolfsson<sup>52</sup> was 79% in cases and 73% in controls, and for Fransson<sup>54</sup> 85% in cases and 49% in controls. The results for these two groups are shown in Table 1.

These results suggest that hesitancy, urgency, leakage, and frequency are more prevalent in cancer patients than controls, but that a weak stream is not; the results for dysuria are contradictory. However, the high prevalence of these symptoms in the general population, allied with the relative rarity of cancer, means that the predictive value of any of these symptoms — which were not reported — will be very small. Thus, there is no evidence from these (or any other) studies that urinary tract symptoms are associated with early prostate cancer. Furthermore, as the controls were healthy, as opposed to patients with BPH, they do not answer the question of whether symptoms are more (or less) common in prostate cancer than BPH. It is probable that T2 tumours — as well as T1 tumours — are symptomless, and that both BPH and T3 or T4 tumours are associated with LUTS. Even so, it is hard to escape the conclusion that no urinary symptoms are sufficiently sensitive and specific to help in the diagnosis of prostate cancer.<sup>56</sup>

### Rectal examination in a patient with LUTS

A rectal examination is performed to assess the size and texture of the prostate gland, and also to identify any local abnormalities in its periphery. Thus, the usual management of a man with LUTS includes a rectal examination and a PSA test.<sup>57,58</sup> The GP performs these to identify BPH or cancer. Although performing these tests may appear illogical when set against the earlier statements that symptoms do not reliably separate cancer from benign causes, there is, how-

ever, one difference. When a man presents with LUTS, he may be seeking a diagnosis, or treatment, or reassurance that he does not have cancer, or any combination of these three.<sup>59</sup> Furthermore, the treatment of an enlarged prostate is different if it contains a cancer to that if it is benign.<sup>60</sup>

No study has reported the predictive value of an abnormal rectal examination in a primary care population, even though it is a commonly performed examination.<sup>61</sup> However, rectal examination was extensively studied as a screening test for prostate cancer.<sup>62</sup> Few of the screening trials reported the prevalence of symptoms in their populations,<sup>62</sup> but those that did described urinary symptoms in over half of their population.<sup>63-65</sup> Having symptoms also increased the likelihood of participating in a screening trial.<sup>66</sup> Thus, results from the screening trials may be of some help in the absence of a primary care study.

An abnormal rectal examination is a strong predictor of cancer. Inter-observer agreement for rectal examination is also high, which increases its value in diagnosis.<sup>67,68</sup> In a meta-analysis of five good-quality screening studies, the following parameters of an abnormal rectal examination for cancer were calculated: sensitivity = 0.64 (95% confidence interval (CI) = 0.47 to 0.80), specificity = 0.97 (95% CI = 0.95 to 0.99), positive predictive value = 0.47 (95% CI = 0.29 to 0.64) and negative predictive value = 0.99 (95% CI = 0.98 to 0.99).<sup>62</sup> However, it is likely that predictive values will be lower when a GP performs the rectal examination, as they will be less experienced than researchers in a screening trial. The positive predictive value of an abnormal rectal examination for cancer decreases with age, because of the increase in benign prostatic masses with age.<sup>69</sup> Some nodules, especially small ones, are foci of BPH, rather than T2 tumours.<sup>70</sup> Two studies reported on whether the positive predictive value calculated from the PSA or rectal examination was higher in patients with urinary symptoms, and found no significant change if the patient had symptoms or not.<sup>63,69</sup> These findings reinforce the earlier point that urinary symptoms are of little help in predicting early cancer.

## PSA testing in a patient with LUTS

Recommendations for PSA testing in men who present to primary care with LUTS are controversial.<sup>58,71</sup> The rationale for measuring the PSA is that prostate cancer will be treated differently to BPH. The disadvantage of PSA measurement in this scenario is the same as that for screening — it may detect stage T1 cancers that would never have given rise to symptoms during the patient's lifetime.<sup>72</sup>

There are no reports on PSA testing in men with symptoms originating from primary care;<sup>41</sup> all studies were from secondary care or from screening trials.<sup>34,73</sup> In a study of 2054 urology outpatients with LUTS, 680 had a PSA above 3.0 µg/l and 131 (6.8%) had prostate cancer diagnosed.<sup>34</sup> The authors emphasised the need for both rectal examination and PSA testing in such men.<sup>34,73</sup> However, this yield of cancers has to be compared with screening of asymptomatic men, where 2.6–4.6% of men have a cancer diagnosed after investigation of a raised PSA.<sup>63,69,74</sup> The screening studies and the outpatients study were carried out on different populations, but taken together the results suggest that for prostate cancer uncovered by PSA testing of men with LUTS, the cancer did not cause the symptoms.

## Conclusion

Prostate cancer is under-researched in primary care. There is a need for descriptive studies of the predictive values of rectal examination and PSA testing in patients with LUTS. Negative predictive values are as important to the patient as positive ones. Such studies must also include the pathway for diagnosis of the cancer, as patients diagnosed with cancer following a screening PSA, or a routine prostatectomy, will have different symptom patterns to those presenting to the GP with urinary problems.

Nonetheless, some reasonable conclusions can be drawn. Early prostate cancer (T1 and T2) does not cause LUTS, as shown by the absence of a link between LUTS and cancer in the screening trials. Locally advanced cancer (T3 and T4) may cause LUTS, but the symptoms of locally advanced cancer are similar to those of BPH. Rectal examination and PSA testing is the only method of discriminating benign from malignant disease with reasonable evidence — but even this does not originate in primary care. Although PSA testing of men with LUTS will uncover some cancers that are clinically insignificant — a main criticism of screening — it will lead to accurate diagnosis, and treatment, of other, locally advanced, cancers.

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